Europäisches Patentamt
European Patent Office
Office européen des brevets

(19)

(11) Publication number: 0 180 276 A1

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 85201677.3

(22) Date of filing: 14.10.85

(51) Int. Cl.⁴: C 07 F 9/15, C 07 B 57/00, C 07 C 101/04, C 07 C 93/14

(30) Priority: 24.10.84 NL 8403224

(43) Date of publication of application: 07.05.86 Bulletin 86/19

(84) Designated Contracting States: BE CH DE FR GB IT LI LU NL SE

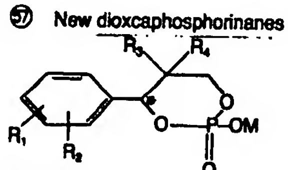
(71) Applicant: Océ-Andeno B.V., Grubbenvorsterweg 8, NL-5928 NX Venlo (NL)

(72) Inventor: Wijnberg, Hans, Huygensweg 4, NL-9752 PA Haren (NL)
Inventor: Ten Hoeve, Wolter, Spiraealaan 56, NL-9741 PD Groningen (NL)

(74) Representative: Bleukx, Lucas Lodewijk Maria, Ir., Océ-Nederland B.V. Patents & Information Dept. Postbus 101, NL-5900 MA Venlo (NL)

(54) Dioxaphosphorinanes, their preparation and use for resolving optically active compounds.

(57) New dioxcaphosphorinanes having the formula:



in which:

M denotes a hydrogen atom or a metal or ammonium ion,

R1 and R2 denote a hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms, an alkoxy group having 1 up to 4 carbon atoms, a nitro group or together denote a methylene dioxy group and

R3 and R4 denote hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms or together denote a cyclohexyl group, one at most of the groups R3 and R4 denoting a hydrogen atom.

A process for the preparation of these dioxaphosphorinanes from a substituted 1-phenyl-1,3-dihydroxypropane by reacting this product with phosphoryl choride, the resolution of the dioxaphosphorinanes in optical isomers by reacting with an optically active amino compound and the resolution of racemates of a plurality of amino compounds, such as hydroxyphenylglycine and phenylalanine, in optically active isomers by reacting with said dioxaphosphorinanes are described.

EP 0 180 276 A1

8423
0180276

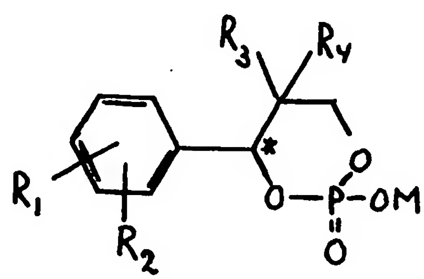
Dioxaphosphorinanes, their preparation and use for resolving optically active compounds

This invention relates to novel dioxaphosphorinanes, the preparation of these compounds, and their use for resolving racemates of optically active amino-compounds into the individual optical isomers.

Several optically active acids are known which can be used as resolving agents for racemates of optically active amino-compounds, including amino-acids. Optically active amino-compounds are used on the one side for separating specific racemates of optically active acids and on the other side as an intermediate for the preparation of pharmaceuticals, inter alia. Examples of the latter use are phenylglycine, parahydroxyphenylglycine, 2-aminobutanol-1 and 2-amino-1-phenyl-1,3-propanediol.

Optically active acids are expensive generally; an additional factor is that they have to be prepared by a complex process. Moreover, these optically active resolving agents are not always proof against racemization in an acidic and/or alkaline medium and they are often difficult to recover after use. Also they are generally only suitable for separating a small number of racemates of optically active amino-compounds. For this reason attempts are continually being made to find optically active acids without the above disadvantages.

The compounds according to the invention are dioxaphosphorinanes having the general formula I



I

in which:

- M denotes a hydrogen atom or a metal or ammonium ion,
- R1 and R2 denote a hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms, an alkoxy group having 1 up to 4 carbon atoms, a nitro group or together denote a methylene dioxy group

and

- R3 and R4 denote a hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms or together denote a cyclohexyl group, one at most of the groups R3 and R4 denoting a hydrogen atom.

These compounds are simple and cheap to prepare, are easily resolved into optical isomers, are very resistant to racemization in an alkaline and acidic medium and are also easy to recover.

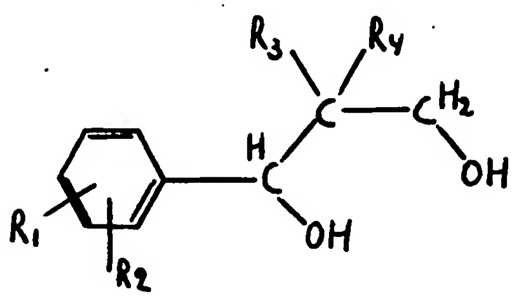
The compounds according to the invention also have the advantage of being available in both the + and the - form. This is in contrast to the optically active compounds derived from natural products, of which generally only one of the isomers is available.

Particularly suitable are the above compounds in which:

- R1 and R2 denote a hydrogen or chlorine atom, a methyl, ethyl, methoxy, ethoxy or nitro group or together denote a 3,4-methylene dioxy group and
- R3 and R4 denote a hydrogen atom, a chlorine atom, a methyl group or together denote a cyclohexyl group.

Examples of suitable compounds are given in Table I.

The racemic dioxaphosphorinanes according to the invention can be prepared by reacting a racemic diol, having the general formula II



II

in wich R1 up to R4 have the same meanings as in formula I, with phosphoryl chloride and hydrolyzing the resulting product in an alkaline medium.

The diols according to formula II are largely known compounds which can be obtained in known manner. In cases where R3 and R4 in formula II denote an alkyl group, such as methyl and ethyl, a mixed aldol condensation, for example, can be used by reacting 1 equivalent of an aromatic aldehyde with two equivalents of a dialkyl acetaldehyde in the presence of 1 equivalent of potassium hydroxide in alcoholic medium. This first results in an aldol which is reduced to a 1,3-diol

by the excess of dialkyl acetaldehyde. This reaction is described inter alia in US Patent 3 092 639. In cases in which R3 and R4 respectively denote a hydrogen and a halogen atom, the 1,3-diols can easily be prepared by reacting N-chlorosuccinic acid imide, or bromine with 3-phenyl-allyl alcohol. These processes are described in Dolby L.J., Wilkens C, Frey T.G, Journal Org. Chem. 31 (1966), 1110 and Bretschneider H, Karpitschka N, Monatsch. Chem. 84 (1953) 1043.

The optical isomers of the dioxaphosphorinanes according to the invention can be separated from the corresponding racemate with optically active amino-compounds such as (-)-ephedrine, (+)-2-amino-1-phenyl-1,3 propanediol, (-)-2-amino-1-butanol and (-)-para-hydroxyphenylglycine.

For the said compounds Table I indicates the optically active amines that can be used to separate the relevant optically active dioxaphosphorinanes from one another inter alia.

The optically active isomers of the dioxaphosphorinanes according to the invention can be used for separating the optically active isomers of various amino-compounds used inter alia as an intermediate for the preparation of pharmaceutical products. Although it is not possible to separate the optical isomers of any amino-compound with just a single dioxaphosphorinane according to the invention, dioxaphosphorinanes are fairly universally usable.

For example, using 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-methoxyphenyl)-2-hydroxy-2-oxide (compound 3 in Table I) it is possible to separate the optically active isomers of phenylalanine, S-(amino-iminomethyl)-β-mercaptobutyric acid, parahydroxyphenylglycine, 1-phenyl-2-paramethoxyphenyl-ethylamine and N-[1-(4'-methoxyphenyl)-isopropyl]-N-ethyl-amine.

The 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-chlorophenyl)-2-hydroxy-2-oxide (compound 9 in Table I) is suitable not only for resolving the above five amino-compounds into their optical isomers, but also for resolving 1,2,3,4-tetrahydro-5-methoxy-N-propyl-2-naphtalene-amine and 1,2-di-(4'-chlorophenyl)-1,2-diamino-ethane.

A third compound suitable for resolving parahydroxyphenylglycine, which is very important for the preparation of pharmaceutical products, is 1,3,2-dioxaphosporinane, 5,5-dimethyl-4-(2',4'-dichlorophenyl)-2-hydroxy-2-oxide (compound 11 in Table I) which has also been

TABLE I

No. M=H	R1	R2	R3	R4	racemate melting point	resolved into optical isomers with	melting point of crytallised optical isomer	Absolute rotation [A]$_{578}$ of the optical pure forms
1	H	H	CH_3	CH_3	224-224.5	B	230-231	60.1
2	2-NO_2	H	CH_3	CH_3		D	229.5-230.5	489
3	2-OCH_3	H	CH_3	CH_3	204-205	A	195-197	63.8
4	4-OCH_3	H	CH_3	CH_3	195-196.5	A,B	203.5-204.5	68.3
5	3,4-OCH_2O-		CH_3	CH_3	200-201.5	A	201	59.2
6	4-Cl	H	CH_3	CH_3	222-223	A,B,C	217-218	59.5
7	H	H	Cl	H	174-178	A,B		
8	H	H	Br	H	190-192.5	A		
9	2-Cl	H	CH_3	CH_3	221.5-225.5	A,D	225.5-227	49.3
10	2-OC_2H_5	H	CH_3	CH_3	194-195	A,D	215.5-216.5	60.9
11	2-Cl	4-Cl	CH_3	CH_3	212.5-213	A,B	238.5-240.5	46.6
12	2-Cl	6-Cl	CH_3	CH_3	212-213	A	256-258	36.8
13	3-NO_2	H	CH_3	CH_3	209-213	A,D	242-250	56.9
14	4-CH_3	H	CH_3	CH_3	219-221	B	220-222	66.9
15	2-Cl	H	cyclohexyl		224.5-225.5	A,D	246.5-247.5	29.5

A = (-)-ephedrine
B = (+)-2-amino-1-phenyl-1,3-propanediol
C = (-)-2-amino-1-butanol
D = (-)-para-hydroxyphenylglycine

found very suitable for resolving 1,2-di(4'-chlorophenyl)-1,2-diaminoethane and 1-phenyl-2-para-methoxyphenyl-ethylamine.

The universal usability is further enhanced by the fact that a choice can be made from a wide range of optically active dioxaphosphorinanes.

The invention will be explained in detail with reference to the following examples.

Example I

Preparation of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-chlorophenyl)-2-hydroxy-2-oxide. (Compound 9 in Table I).

A solution of 141.0 g (0.92 mole) of phosphoryl chloride in 250 ml of dichloromethane was added over a period of 1 hour with agitation to 183.1 g (0.854 mole) of 1-(2'-chlorophenyl)-2,2-dimethyl-1,3-dihydroxypropane in 400 ml of dichloromethane. The mixture was heated with reflux for 4 hours and then concentrated by evaporation. The resulting residue was heated with agitation with a solution of 100 g of sodium hydroxide (2.5 mole) in 1 litre of water until a substantially clear liquid was obtained. The mixture, from which a granular substance rapidly separated, was cooled to 70°C and mixed with 290 ml of concentrated hydrochloric acid. An oil formed, which rapidly solidified. After filtering off the remaining liquid, washing with water and ether, followed by drying at 80°C, 201.6 g (0.729 mole) of the above dioxaphosphorinane was obtained, equivalent to an 85% yield.

Example II

Preparation of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-methoxyphenyl)-2-hydroxy-2-oxide. (Compound 3 in Table I).

A mixture of 122 g (0.796 mole) of phosphoryl chloride in 250 ml of dichloromethane was added over a period of half an hour with cooling to 163.5 g (0.779 mole) of 1-(2'-methoxyphenyl)-2,2-dimethyl-1,3-dihydroxy-propane and 168.7 g (1.67 mole) of triethylamine in 350 ml of dichloromethane. After 4½ hours' heating with reflux, the reaction mixture was twice extracted with 750 ml of water. The water layers were extracted with 300 ml of dichloromethane.

All the dichloromethane fractions were dried on sodium sulphate and concentrated by evaporation. The remaining oil was heated with a solution of 88 g (2.2 mole) of sodium hydroxide in 800 ml of water

until a clear solution formed. This solution was cooled and 250 ml of concentrated hydrochloric acid was added at 40°C. The result was an oil which solidified on further cooling. After removal of the liquid, washing with water and ether, and drying 173.3 g (0.637 mole) of the above dioxaphosphorinane was obtained. The yield was 83%.

Example III

The compounds 1,2,6,11,12,13 and 15 of Table I were prepared in the same way as in Example I from the corresponding diol.

Example IV

The compounds 4,5,10 and 14 of Table I were prepared in the same way as in Example II from the corresponding diol.

Example V

Preparation of 1,3,2-dioxaphosphorinane, 5-bromo-4-phenyl-2-hydroxy-2-oxide. (Compound 8 in Table I).

A mixture of 18.5 g (0.121 mole) of phosphoryl chloride and 50 ml of dichloromethane was added over a period of 15 minutes to a mixture of 23.1 g (0.100 mole) of 2-bromo-1-phenyl-1,3-propanediol, 18.1 g (0.229 mole) of pyridine and 200 ml of dichloromethane. The mixture was heated with reflux for 3 hours and washed twice with 250 ml of water. The water layers were extracted with 150 ml of dichloromethane. The dichloromethane fractions were dried on sodium sulphate and then concentrated by evaporation. The resulting residue was mixed with 12.5 g (0.313 mole) of sodium hydroxide and 200 ml of water and was heated for 1½ hours at a temperature of 65 - 70°C. After cooling to 20°C the resulting solution was acidified with 50 ml of concentrated hydrochloric acid. The precipitated dioxaphosphorinane was sucked off and washed with water and ether. The yield was 23.9 g (81.6 m mole) equivalent to an 82% yield.

Example VI

Resolution of the optical isomers of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-ethoxyphenyl)-2-hydroxy-2-oxide. (Compound 10 in Table I).

A mixture of 115.4 g (0.403 mole) of the racemate of compound 10 and 68.0 g (0.407 mole) of (-)-parahydroxyphenylglycine was dissolved with heating in 1400 ml of a 1:1 mixture of water and ethanol. The solution was cooled by leaving it at room temperature for 5 hours with

agitation and the occasional addition of seed crystals. The diastereomeric salt which crystallized out was filtered off and washed with 250 ml of water. After drying the weight was 66.8 g (0.147 mole) and the optical rotation $[\alpha]_{578}$ = -98.5. The yield was 37%. The diastereomeric salt obtained in this way was agitated for 5 hours with a mixture of 30 ml of concentrated hydrochloric acid and 300 ml of water. After filtration and drying, 42.0 g (0.147 mole) of dioxaphosphorinane with an optical rotation $[\alpha]_{578}$ = -60.9 was obtained. Hydrolysis of the filtrate remaining after filtration of the diastereomeric salt, known as the main filtrate, yielded 61.6 g of dioxaphosphorinane with an optical rotation $[\alpha]_{578}$ = + 37.0. $[\alpha]_{578}$ here and hereinafter is given for C = 0.5 g per 100 ml solution in methanol unless otherwise stated.

Example VII

Resolution of the optical isomers of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-phenyl-2-hydroxy-2-oxide (Compound 1 in Table I).

A mixture of 24.2 g (0.1 mole) of the racemate of compound 1 and 16.7 g (0.1 mole) of (+)-2-amino-1-phenyl-1,3-propanediol was dissolved by heating in 200 ml of ethanol. The solution was concentrated by evaporation and 11.9 g of diastereomeric salt was obtained therefrom after cooling. The filtrate was further concentrated by evaporation and combined with a mixture of 122 g (0.504 mole) of racemate of compound 1, 85 g (0.509 mole) of (+)-2-amino-1-phenyl-1,3-propanediol and 450 ml of ethanol. After heating until dissolution, the mixture was cooled by leaving it at room temperature for 12 hours with agitation. The precipitated salt was filtered off, washed with water and ether and dried. In this second step, 46.85 g of diastereomeric salt with an optical rotation $[\alpha]_{578}$ = -15.7 was obtained. Another 31.7 g of diastereomeric salt with $[\alpha]_{578}$ = -11.2 was crystallized out of the washing liquids and the main filtrate by concentrating by evaporation and cooling to -15°C , and yielded 20.5 g of pure diastereomeric salt by recrystallization with 80 ml of ethanol. The total production of crystallized-out diastereomeric salt was 79.26 g (0.194 mole). The yield was 32%.

The 46.85 g of diastereomeric salt from the second step were converted with a 100% yield into the free dioxaphosphorinane by treatment

with 150 ml of hydrochloric acid in 300 ml of water. The optical rotation was -60.1 ($[\alpha]_{578}$, C = 1, CH_3OH).

From the remaining filtrate of the third step it was possible after considerable concentration by evaporation to filter off a portion of salt which after hydrolysis yielded 32.86 g of dioxaphosphorinane with $[\alpha]_{578}$ = 37.0.

After further concentration of the remaining filtrate, another portion of salt was obtained which after hydrolysis yielded 43.0 g of dioxaphosphorinane with $[\alpha]_{578}$ = + 42.9. Recrystallization of the latter two portions from a 3:1 mixture of ethanol and water yielded 23.47 g and 31.61 g respectively of purified dioxaphosphorinane with $[\alpha]_{578}$ = + 54.2 and 60.2 respectively.

Example VIII

Resolution of the optical isomers of 1,3,2-dioxaphosphorinane, 5,5-dimethy-4-(2'4'-dichlorophenyl)-2-hydroxy-2-oxide. (Compound 11 in Table I).

A mixture of 285.5 g (0.918 mole) of the dioxaphosphorinane and 155 g (0.939 mole) of (-)-ephedrine was dissolved with heating in 500 ml of ethanol. The solution was cooled to 20°C with agitation. Agitation was continued for another 4 hours and then the mixture was left to stand for 12 hours. After filtration of the precipitate, washing with ether, recrystallization from 430 ml of ethanol and drying, 118.5 g (0.249 mole) of diastereomeric salt was obtained with an optical rotation $[\alpha]_{578}$ = + 6.2. The yield was 27%. Using 117 g, hydrolysis with 50 ml of concentrated hydrochloric acid in 450 ml of water gave 75.45 g (0.243 mole) of dioxaphosphorinane with an optical rotation $[\alpha]_{578}$ = + 46.6. The yield was 97%.

From the main filtrate, after evaporation of 250 ml of ethanol, a diastereomeric salt was precipitated which, after filtration, washing with ether and drying, weighed 52.5 g (0.110 mole) and had an optical rotation $[\alpha]_{578}$ = -44.0. Hydrolysis of this product with 20 ml of hydrochloric acid in 180 ml of water yielded 32.4 g (0.104 mole) of dioxaphosphorinane with $[\alpha]_{578}$ = - 43.2.

Example IX

Resolution of the optical isomers of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'chlorophenyl)-2-hydroxy-2-oxide. (Compound 9 in Table I).

A mixture of 169.9 g (0.615 mole) of racemate of compound 9 and 102.7 g (0.615 mole) of (-)-parahydroxyphenylglycine was dissolved with heating in a mixture of 1030 ml of 96% ethanol and 800 ml of water. The mixture was cooled by leaving it at room temperature with agitation and occasional addition of seed crystals. Agitation was then continued for 12 hours and the precipitated diastereomeric salt was filtered off, washed with 300 ml of water and dried. The production was 103. 6 g (0.234 mole), equivalent to a 38% yield. The optical rotation was - 95.7 $[\alpha]_{578}$).

The resulting diastereomeric salt was hydrolyzed by agitating it for 6 hours with 105 ml of concentrated hydrochloric acid and 465 ml of water. After filtration, washing with water and drying, 58.8 g of dioxaphosphorinane were obtained (91% yield) with an optical rotation $[\alpha]_{578}$ = - 49.3.

The main filtrate after the treatment with para-hydroxyphenylglycine was left to stand for 2 days and then agitated for 7 hours with 150 ml of concentrated hydrochloric acid. After suction filtration, washing and drying, 74.3 g of dioxaphosphorinane was obtained with $[\alpha]_{578}$ = + 48.9.

Example 10

Resolution of the optical isomers of 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-nitrophenyl)-2-hydroxy-2-oxide. (Compound 2 in Table I).

A mixture of 58.6 g (0.204 mole) of the racemate of compound 2 and 34.2 g (0.205 mole of (-)-parahydroxyphenylglycine was dissolved with heating in 600 ml of a 1:1 mixture of water and absolute alcohol. The mixture was cooled by leaving it at room temperature with agitation and occasional addition of seed crystals. After 12 hours' agitation, the precipitated diastereomeric salt was filtered off, washed with water and dried at 75°C. The yield was 40.5 g (89.2 mole, 44%). The optical rotation of the salt $[\alpha]_{578}$ = -353.

39.95 g of the resulting salt was agitated for 7 hours with 45 ml of concentrated hydrochloric acid in 135 ml of water. The precipitated dioxaphosphorinane was filtered off and washed and after drying weighed 23.6 g (82.2 m mole, 94%) and $[\alpha]_{578}$ was -463.

After the treatment with para-hydroxyphenylglycine the main

filtrate, after decomposition with hydrochloric acid, yielded 27.7 g of dioxaphosphorinane with $[\alpha]_{578}$ = + 409. Recrystallization of this product with CH_3OH yielded 17.73 g with $[\alpha]_{578}$ = +489. Over 6 g of the dioxaphosphorinane with positive rotation were additionally obtained after concentrating the filtrate by evaporation.

It was found that the resolutions according to Examples VI up to X are reversible, i.e. the optical isomers of the relevant amine can be separated with the relevant dioxaphosphorinane.

Example XI

Resolution of the optical isomers of phenylalanine with (-)-1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-chlorophenyl)-2-hydroxy-2-oxide. (Compound 9 in Table I).

A mixture of 8.80 g (31.8 m mole) of the (-) form of the dioxaphosphorinane and 5.25 g (31.8 m mole) of phenylalanine racemate was dissolved with heating in 60 ml of water and 25 ml of absolute alcohol. The mixture was cooled by leaving it at room temperature with agitation and the occasional addition of seed crystals. After 5½ hours' agitation the precipitate was filtered off, washed with water and dried. The yield was 6.03 g (13.7 m mole) equivalent to a 43% yield. The $[\alpha]_{578}$ of the precipitate was -26.6. Of this product 5.87 g (13.3 m mole) were hydrolyzed by agitation for 7 hours with 7 ml of concentrated hydrochloric acid and 63 ml of water. The dioxaphosphorinane re-liberated in this way was filtered off and washed and after drying weighed 3.5 g (12.7 m mole). This means that 95% was recovered. The filtrate was dissolved in a mixture of 10 ml of water and 5 ml of ethanol and neutralized with a dilute sodium hydroxide solution. The resulting precipitate consisted of 1.1 g (+)-phenyl-alanine with $[\alpha]_{578}$ = + 34.2 (C = 1.96, H_2O).

The remaining filtrate after concentration by evaporation and purification over a Dowex $-H^+$ column yielded another 0.75 g phenylalanine with $[\alpha]_{578}$ = + 32.8.

The total yield was 1.85 g (11.2 m mole) equivalent to 84%.

Example XII

Resolution of the optical isomers of 1-phenyl-2-paramethoxyphenyl-ethylamine with (+)- 1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-4'

-dichlorophenyl)-2-hydroxy-2-oxide. (Compound 11 in Table I).

A mixture of 12.5 g of the impure amine and 14.5 g (46.6 m mole) of the dioxaphosphorinane was heated with 105 ml of methanol for 60 hours with agitation. From the mixture it was possible to recover 8.14 g (15.1 m mole, 32%) of the diastereomeric salt with $[\alpha]_{578}$ = + 76.9. Of this product, 7.93 g were agitated with 150 ml of 1N sodium hydroxide solution. After agitating the suspension for 16 hours, 50 ml of chloroform were added and after agitation for another half hour the solid was filtered. From this solid, which consisted of the sodium salt of the dioxaphosphorinane, the free acid can be recovered after acidification. The filtrate, which consisted of two layers, was separated by means of a separating funnel. The aqueous layer was extracted with 40 ml of chloroform and the chloroform layer was washed with water. The chloroform fractions were dried, concentrated by evaporation and purified by Kugelrohr distillation at 135°C under a pressure of 0.03 mm Hg. This yielded 3.05 g of colourless amine (13.4 m mole) equivalent to 91% yield). The $[\alpha]_{578}$ was + 64.3 (C = 1.07, CH_3OH).

Example XIII

Resolution of the optical isomers of the amine of Example XII with (-)-1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-methoxyphenyl)-2-hydroxy-2-oxide. (Compound 3 in Table I).

A mixture of 16.8 g (61.8 m mole) of the dioxaphosphorinane and 15.5 g of the impure amine was dissolved with heating in a mixture of 50 ml of 96% ethanol and 10 ml of water. After cooling, by leaving the mixture to stand for 12 hours with agitation, it was possible to filter off 7.92 g (15.9 m mole) of diastereomeric salt. The yield was 26%. The optical rotation $[\alpha]_{578}$ was - 86.3. Of this product, 7.5 g was agitated for 5 hours with a solution of 4.0 g of sodium hydroxide in 100 ml of water. The liquid was extracted twice with 50 ml of chloroform, washed with 50 ml of water, dried and concentrated by evaporation. Kugelrohr distillation yielded 3.2 g (14.1 m mole, yield 94%) of amine with $[\alpha]_{578}$ = -63.8 (C = 1.11, CH_3OH).

From the aqueous liquid remaining after extraction with chloroform it was possible to recover 14.71 g of dioxaphosphorinane after acidification, equivalent to an 88% yield.

Example XIV

Separation of the optical isomers of methionine with (+)-1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-(2'-chlorophenyl)-2-hydroxy-2-oxide (Compound 9 in Table I).

A mixture of 7.64 g (50.0 m mole) of racemate of methionine and 13.83 g (50.0 m mole) of the (+)-dioxaphosphorinane was dissolved with heating in a mixture of 70 ml of 96% ethanol and 35 ml of water. After cooling the solution with agitation for 5 hours the precipitated diastereomeric salt was sucked off, washed with water and dried. The yield was 5.46 g (12.8 m mole, 26%) with $[\alpha]_{578}$ = + 33.3. This salt was agitated for 4 hours with 45 ml of water, 6 ml of concentrated hydrochloric acid and 10 ml of methanol. From the non-dissolved fraction it was possible to recover 3.42 g (12.4 m mole) of dioxaphosphorinane (96% yield) by filtration, washing with water and drying. The dissolved fraction was concentrated by evaporation, dissolved in water and purified over a Dowex -H^+ column.

After concentration by evaporation of the purified product, 1.6 g (10.7 m mole) of (+)-methionine were obtained with $[\alpha]_{578}$ = + 21.8 (C = 0.797, 0.2N hydrochloric acid). The yield was 84%.

Example XV

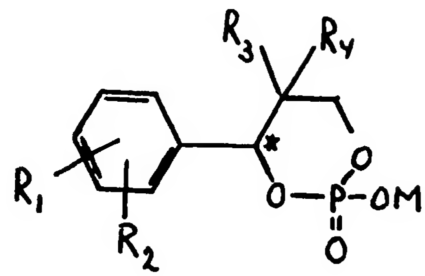
Separation of the optical isomers of 1,2-di(4'-chlorophenyl)-1,2-diamino-ethane by means of (-)-1,3,2-dioxaphosphorinane, 5,5-dimethyl-4-phenyl-2-hydroxy-2-oxide. (Compound 1 in Table I).

A mixture of 12.5 g (44.6 m mole) of the (-)-dioxaphosphorinane and 12.5 g (44.5 m mole) of the diamine was dissolved with heating in 75 ml of 96% ethanol. The mixture was cooled by leaving it to stand for 5½ hours with agitation and the occasional addition of seed crystals. The precipitate was filtered, washed with an ethanol/ether mixture and then with ether and then dried. The production was 6.38 g (12.2 m mole) of diastereomeric salt with $[\alpha]_{578}$ = + 63.8. The yield was 27%. The diastereomeric salt was agitated with 2 g of sodium hydroxide in 50 ml of water. 25 ml of chloroform were then added and agitation was continued for half an hour. After dilution with 50 ml of water and 25 ml of chloroform, the layers were separated. The aqueous phase was extracted with 50 ml of chloroform. The chloroform fractions were washed with water, dried and concentrated by evaporation. The resulting oil, which solidified on cooling, had an $[\alpha]_{578}$ = + 150.2 and weighed 3.38 g (12.0 m mole) equivalent to a 99% yield.

It was possible to recover in all 9.46 g of dioxaphosphorinane (88% yield).

CLAIMS

1. Dioxaphosphorinanes of the general formula I



I

in which:

- M denotes a hydrogen atom or a metal or ammonium ion,
- R1 and R2 denote a hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms, an alkoxy group having 1 up to 4 carbon atoms, a nitro group or together denote a methylene dioxy group and
- R3 and R4 denote a hydrogen atom, a halogen atom, an alkyl group having 1 up to 4 carbon atoms or together denote a cyclohexyl group, one at most of the groups R3 and R4 denoting a hydrogen atom.

2. Dioxaphosphorinanes according to claim 1, having the general formula I in which:

- R1 and R2 denote a hydrogen or chlorine atom, a methyl, ethyl, methoxy, ethoxy or nitro group or together denote a 3,4-methylene dioxy group and
- R3 and R4 denote a hydrogen atom, a chlorine atom, a methyl group or together denote a cyclohexylgroup, one at most of the groups R3 and R4 denoting a hydrogen atom.

3. Dioxaphosphorinanes according to claim 1, having the general formula I in which:

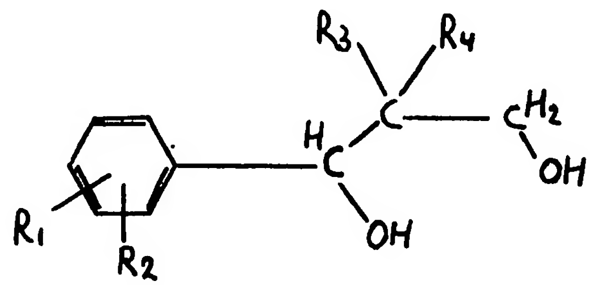
- R1 denotes a hydrogen or halogen atom at the para-position,
- R2 denotes a methoxy group or chlorine atom at the ortho-position and
- R3 and R4 denote a methyl group.

4. Optically active isomers of the dioxaphosphorinanes according to claim 1.

5. Optically active isomers of the dioxaphosphorinanes according to claim 2.

6. Optically active isomers of the dioxaphosphorinanes according to claim 3.

7. A process for the preparation of dioxaphosphorinanes according to claims 1, 2 or 3, characterised in that a diol of the general formula II



II

in which R1 up to R4 have the same meanings as in claims 1, 2 or 3, is reacted with phosphoryl chloride and the resulting product is hydrolyzed in an alkaline medium.

8. A process for the preparation of optically active isomers of a dioxaphosphorinane according to claims 4, 5 or 6, characterised in that the corresponding racemate is reacted in a solvent with an optically active amino-compound to form a diastereomeric salt which at least partially crystallizes out and a diastereomeric salt which remains in solution and after separation of the crystallized-out and dissolved salts one or both salts are hydrolyzed.

9. A process for separating the optically active isomers of an amino-compound from the corresponding racemate, characterised in that the racemate is reacted with an optically active dioxaphosphorinane according to claims 4, 5 or 6 to form a diastereomeric salt which crystallizes out and a diastereomeric salt which remains in solution, the two salts are separated from one another and if necessary hydrolyzed.

10. A process for separating the optical isomers of para-hydroxyphenylglycine, characterised in that the racemate of para-hydroxyphenylglycine is reacted with an optically active

dioxaphosphorinane according to claim 6 to form a diastereomeric salt which crystallizes out and a diastereomeric salt which remains in solution, the two salts are separated from one another and if necessary hydrolyzed.

11. A process for separating the optical isomers of phenylalanine, characterised in that the racemate of phenylalanine is reacted with an optically active dioxaphosphorinane according to claim 6 to form a diastereomeric salt which crystallizes out and a diastereomeric salt which remains in solution, the two salts are separated form one another and if necessary hydrolyzed.

12. A process for separating the optical isomers of 1-phenyl-2-paramethoxyphenyl-ethylamine, characterised in that the corresponding racemate is reacted with an optically active dioxaphosphorinane according to claim 6 to form a diastereomeric salt which crystallizes out and a diastereomeric salt which remains in solution, the two salts are separated from one another and if necessary hydrolyzed.

European Patent Office

EUROPEAN SEARCH REPORT

0180276
Application number

EP 85 20 1677

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	GB-A-1 360 946 (RICHARDSON-MERRELL S.p.A.) * Claims * ---	1-12	C 07 F 9/15 C 07 B 57/00 C 07 C 101/04 C 07 C 93/14
A	BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, vol. 42, no. 6, June 1969, pages 1713-1718; M. KAINOSHO et al.: "Phosphorus-proton spin-spin coupling in the P-O-C-H group. A comparison of cyclic and acyclic systems" * Whole document * -----	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 F 9/00 C 07 B 57/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	20-01-1986	BESLIER L.M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document
T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons
& : member of the same patent family, corresponding document